In overcoming a rejection during prosecution, Janssen relied on a comparison of the dopamine antagonism (determined using the "A" of the ATN test) of Ketanserin and Risperidone, arguing that this property alone was predictive of a compound's antipsychotic activity in humans. *See, e.g., DFF86-DFF88; DFF222 and DFF227.* The '663 patent issued only after Janssen pointed out that Risperidone possessed dopamine antagonism, and Ketanserin did not. *See, e.g., DFF220-DFF228.*[3]

Because of Janssen's statement to the USPTO that dopamine antagonism shown by the ATN test is "predictive" of antipsychotic activity, and that presence (or absence) of dopamine antagonism in prior art compounds, and was necessarily relied on in order to obtain allowance of the '663 patent, Janssen cannot now dismiss the criticality of a prior art compound's dopamine antagonism *via* the ATN test to the current obviousness inquiry.

The foregoing supports the following additional findings of fact:

DFF312. The norepinephrine test (i.e., the "N" part of the ATN test) showed a compound's activity associated with side effects. *See Tr. 543, ll. 2-17; 562, l. 25 to 563, l. 23 (W).*

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[3] Although Ketanserin was not an anticholinergic, Janssen did not argue this distinction to the USPTO. *See DFF314.* Defendants submit that the failure of Janssen to do so provides further support to Defendants' assertion that, in terms of relevance to one skilled in the art, one was not looking for compounds having anticholinergic activity, but for compounds having low EPS *via* any means. Moreover, this emphasizes that a compound's dopamine antagonism was the focus of those skilled in the art in the early 1980s, not anticholinergic activity.

DFF313.

REDACTED

DFF314. Although Ketanserin did not have anticholinergic activity, Janssen did not argue this distinction to the USPTO during the prosecution of the '663 patent. *See, e.g., DTX-176.*

C. THE "CLEAR AND CONVINCING" STANDARD IS FAR EASIER TO MEET BECAUSE OF JANSSEN'S ADMITTED WITHHOLDING OF MATERIAL INFORMATION (*E.G.*, PIRENPERONE'S DOPAMINE ANTAGONISM) FROM THE USPTO

Janssen argues that Defendants rely on the same prior art that was considered by the USPTO, and that deference to the USPTO's decision is thus required. *See, e.g., JFF/CL ¶ 46.* This position is contrary to Defendants' position at trial, the law and the record.

Defendants' obviousness position is not based on the Pirenperone patent *(U.S. Patent 4,342,870, PX-80)*, but on Pirenperone the compound and the properties inherent therein. It is not disputed that the Pirenperone patent did not

disclose all of the properties possessed by the compound Pirenperone, *e.g.*, dopamine antagonism, passed the blood-brain barrier, had low EPS, and had been safely administered to humans. *See DFF85; DFF104-DFF113.* Indeed, Janssen admittedly withheld Pirenperone's dopamine antagonism from the USPTO, and articles confirming Pirenperone's other properties (low EPS, use in humans in the clinic, etc.) were not submitted to the USPTO in the Information Disclosure Statement ("IDS") filed by Janssen during the prosecution of the '663 patent. *See, e.g., DFF229-DFF246.*

As there is absolutely nothing in the '663 patent's prosecution history indicating that the Patent Examiner considered any of the foregoing information, the law considers Defendants' burden to be more easily carried, as its obviousness case is based on information that was not considered by the USPTO. *See, e.g., SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000); *DCL9*.

For Janssen to now argue that the USPTO considered the prior art now relied upon by Defendants is not only a distortion of Defendants' position, but is contrary to the facts established at trial concerning Janssen's admitted failure to bring all of the properties possessed by Pirenperone to the attention of the USPTO.

IV. THE MOTIVATION TO MODIFY PIRENPERONE WAS PRESENT IN THE PRIOR ART–*PRIMA FACIE* OBVIOUSNESS WAS PROVEN

1. Pirenperone Was Known to Have a Short Half-Life

Pirenperone has a short half-life as a matter of fact—Janssen litigation-prompted protestations notwithstanding. Janssen's own dog study, used "to predict the pharmacokinetic behaviour of the compound in man," taught in Janssen's own words "that Pirenperone is short acting." *See DFF118-DFF120*. The human clinical trials were consistent and demonstrated that even with increased, large doses of Pirenperone, a regimen of administering Pirenperone three times per day was maintained. *See DFF116-DFF117*. Again, such a result in man was expected, as the Janssen dog study found that even with doses four times that required to see an effect in 50% of the dogs, the maximum duration of action was only four hours. *See DFF118.*

2. In the Field of Antipsychotic Drugs, Three Times Per Day Dosing was "Short-Acting"—Once Per Day Dosing Was Desired

Janssen now argues that three times per day dosing does not signal that a compound is "short-acting." This argument flies in the face of Janssen's own internal reports that state that Pirenperone was "short-acting," as discussed *supra*. Further, Janssen discontinued the development of Pirenperone as an antipsychotic because of the very fact that Pirenperone had such a short half-life. *See DFF125*.

Also, the fact that in the field of antipsychotics once per day dosing was desired was established by Janssen's own testimony. *See, e.g., DFF124.*

Janssen quotes Dr. Wolff's testimony that three times per day dosing is a matter of desire, and not a requirement. Indeed, antipsychotics existed with three times per day dosing or longer. But those developing a new antipsychotic had as a goal once per day dosing. *See PX 276.* This again, was established by Janssen's own pre-litigation actions.

As for Dr. Wolff's testimony about dosing being a matter of choice, again Janssen fails to quote his specific testimony regarding antipsychotic dosing:

> Q. You have no basis to disagree that if you came out with the first atypical for general use, after 26 years, that three times a day dosing could be acceptable. You can't disagree with that, can you?
>
> A. Well, I think I can, because that is a vulnerable product. If you have a three times a day product and the next one that comes out is a once a day you are very vulnerable.

Dr. Wolff's testimony confirms that once a day dosing would have been desired. *See DFF315.*

The foregoing supports the following additional finding of fact:

DFF315. Dr. Wolff's testimony confirmed that once a day dosing would have been desired in an antipsychotic in the early 1980s, explaining that a product requiring three time per day dosing would be "very vulnerable" to a product that required one once per day dosing. *See Tr. 648, l. 21 and 649, l. 3 (W).*

3. Hindsight Was Not Required to Modify the Keto Group

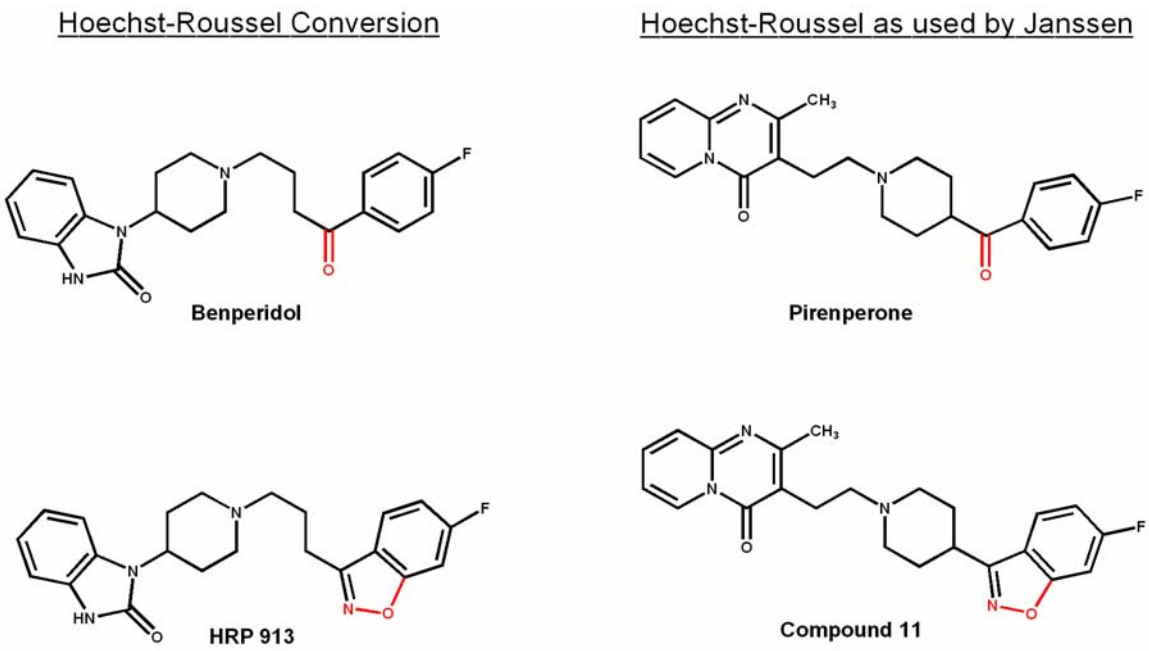
Despite the unabashed admission by Mr. Kennis who, when discussing the metabolism of Pirenperone at the keto group, confirmed this to be well known in the prior art by stating "there is literature on it," Janssen persists in arguing that one of ordinary skill in the art would not immediately suspect the keto group as the source of the short half-life. *See DFF132(revised) (Kennis Dep. 72, ll. 1-12.)* Moreover, Janssen's own closely related compound Ketanserin was known to have suffered the same problem, metabolism at the keto group, and would have been viewed by one of ordinary skill in the art as being indicative of the source of the problem with Pirenperone. *See DFF129-DFF130.*

The foregoing supports the following revised finding of fact (revised to address a typographical error in the citation included in the original finding):

FF132(revised). Again perhaps the most telling of all was the deposition testimony of Mr. Kennis, an inventor of the '663 patent who did not testify at trial. Upon being presented with the structure of Pirenperone, Mr. Kennis immediately confirmed that the presence of the keto group on Pirenperone was responsible for the short half-life, stating that "there is literature on it." *Kennis Dep. 72, ll. 1-12.*

4. The Choice of the Benzisoxazole Was Motivated by the Prior Art

As the Court is aware, the change from the keto group to a benzisoxazole was taught to Janssen and others as shown by the following figure:



While Janssen (correctly) admits that the law presumes that the person having ordinary skill knows all of the prior art (*see JFF/CL ¶ 61*), Janssen alleges that he or she is not an innovator and can make no inferences based on the prior art. *See JFF/CL ¶ 62*. In support, Janssen cites a single line from the *Standard Oil* decision, *i.e.*, wherein the ordinarily skilled artisan is characterized as "one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient ... systematic research or by extraordinary insights." *See JFF/CL ¶ 63*. Once again, Janssen presents its position out of context.

A close reading of *Standard Oil* reveals that its use of the term "innovation" is not equated with following teaching that is provided by the prior art, but is instead associated with a very high level of skill attributable to an "inventor," *i.e.*, one involved in "*systematic* research" or "*extraordinary* insights" (emphasis

added.) As confirmed by Dr. Wolff, the only expert who testified at trial having (decades) of real-world experience in pharmaceutical drug discovery, one skilled in the art in the 1980s need not have been an innovator in order to understand and be motivated by the teaching provided by the prior art to select Pirenperone for development as an antipsychotic, or to understand and be motivated by the prior art to modify Pirenperone in a manner which yields Compound 11. *See, e.g., Section II.B.2.b.-g. of Defendants' FF/CL; DFF191; DFF316 and DFF317.* Indeed, even Dr. Meltzer agreed that one of ordinary skill in the art would possess intelligence and creativity. *See DDF320.*

It is significant that the Federal Circuit *affirmed* the district court's obviousness decision in *Standard Oil*. Thus, *Standard Oil* undercuts Janssen's argument, confirming instead that even the ordinarily skilled artisan "who thinks along the line of conventional wisdom"—one who follows the prior art but does not "innovate"—is not simply a mindless "pair of hands," but has more than sufficient technical insight to undertake modifications taught by the prior art. This is exemplified in *Standard Oil*, wherein the claim found obvious was directed to a one-step chemical process. The Federal Circuit concluded that one skilled in the art would have been able to understand and combine the teachings of prior art references and found the claim invalid on that basis. Indeed, *Standard Oil* confirms that one of ordinary skill in the art would have followed the prior art teaching, and dismissed an argument by the patentee (similar to the

unpredictability argument raised by Janssen here) that catalytic reactions were unpredictable.

Because Defendants have identified a multitude of prior art references which would have taught one skilled in the art why and how Pirenperone should be modified with a reasonable expectation of success, there is no question that going beyond the conventional wisdom (*e.g.*, by ignoring what is taught in the prior art, undertaking systematic research and/or using extraordinary insights), would not have been needed for one of ordinary skill to use those teachings to make Compound 11 from Pirenperone. As Dr. Wolff confirmed, there was "ample precedent in the literature for the success of this replacement," and that the literature did not need to recite the term "bioisoteric" in order to provide this teaching to one of ordinary skill in the art—"a rose by any other name would smell as sweet." *See DFF318.*

Janssen also argues that rather than modifying Pirenperone, one could reformulate the compound into a controlled release dosage form. First, whether an alternate means (controlled release) to solve a problem (short half-life) exists does not make an obvious choice (converting the keto group to a benzisoxazole) less obvious. *See, e.g., Fulton,* 391 F.3d at 1200 (an obviousness determination need not be based on the preferred or most desirable combination——the question is whether there is something in the prior art to suggest the desirability, and thus the obviousness, of making the combination). Moreover, the fact remains that in the

field of antipsychotics, no one has yet formulated a controlled release product. As Dr. Meltzer testified, "I don't think there are any controlled release antipsychotics." *See DFF319.*

The foregoing supports the following additional findings of fact:

DFF316. As confirmed by Dr. Wolff, the only expert who testified at trial having (decades) of real-world experience in pharmaceutical drug discovery, one skilled in the art in the 1980s (i.e., not an innovator) would have been motivated by the teaching provided by the prior art to select Pirenperone for development as an antipsychotic. *See, e.g., Tr. 550, l. 13 to 551, l. 3 (W).*

DFF317. As further confirmed by Dr. Wolff, the only expert who testified at trial having (decades) of real-world experience in pharmaceutical drug discovery, one skilled in the art in the 1980s (i.e., not an innovator) would have been motivated by the teaching in the prior art to modify Pirenperone in a manner that yields Compound 11. *See, e.g., Tr. 549, ll. 2-24; 572, l. 14 to 573, l. 12; 578, ll. 1-4; 593, l. 7 to 594, l. 1 (W).*

DFF318. Dr. Wolff confirmed that, with regard to the replacement of the keto group in Pirenperone with a benzisoxazole group, there was "ample precedent in the literature for the success of this replacement," and that the literature did not need to recite the term "bioisosteric" in order to provide this teaching to one of ordinary skill in the art—"a rose by any other name would smell as sweet." *See Tr. 670, ll. 8-25 (W).*

DFF319. In the field of antipsychotics, no one has yet formulated a controlled release product. *See Tr. 306, ll. 6-7 (M).*

DFF320. In describing the characteristics possessed by one of ordinary skill in the art, Dr. Meltzer confirmed that such a person would indeed have creativity, testifying that "it is not necessarily the degree, it is the intelligence and the creativity of the individual." *See Tr. 266, ll. 9-12; Tr. 286, ll. 7-13.*

5. Wolff Did Not Admit That the Likelihood of Success in Making the Keto to Benzisoxazole Conversion Was 5-10%

Dr. Wolff was the only expert experienced in drug development during the period in question. According to Dr. Wolff, there was ample basis for one skilled in the art to refer to other prior art ketone and benzisoxazole compounds when assessing the expectation of success concerning the modification of Pirenperone. Dr. Wolff assessed the likelihood of success to be more than a reasonable expectation, exceeding 60 percent. *See DFF144.* Once again, Janssen attempts to lead the Court astray by arguing that Dr. Wolff testified that the likelihood of success in making the keto to benzisoxazole conversion (transforming Pirenperone into Compound 11) was 5-10 percent. *JFF/CL ¶ 167.* Nothing could be further from the truth. Under cross examination by Mr. Diskant regarding Dr. Wolff's prior actual experience in making unspecified changes to unspecified molecules for unspecified reasons, Dr. Wolff testified that he had "a modest success rate." *See Tr. 651, l. 14 (W).* Then, the following exchange occurred.

Q. So when you have been saying you make this change with a reasonable expectation of success you are talking about five to ten percent, something like that?

A. We are talking about different things. Are you talking specifically about the benzisoxazole modification?

Q. Not yet, no.

Tr. 651, ll. 16-21.

So, as Janssen well knows, Dr. Wolff never testified that as to the specific issue in this case, replacing Pirenperone's keto group with a benzisoxazole, there would be a 5-10 percent chance of success. As Dr. Wolff explained, "We are talking about different things." *See Tr. 651, ll. 16-21.* When asked on redirect about his opinion regarding the expectation of success on the only issue important to this case, converting the Pirenperone keto group to a benzisoxazole, his response was as follows:

> For that particular conversion I think the likelihood of success would be quite high because we have precedent in three different pharmacological classes, one of which is the neuroleptics themselves. We have several examples in the neuroleptics, that the benzisoxazoles maintains activity. So I think the likelihood of success would be, you know, high, perhaps 60, 70 percent.

See DFF144.

None of Janssen's experts were qualified to contradict Dr. Wolff's testimony concerning drug development in the early 1980s. There is nothing in the record

indicating that Dr. Meltzer, a psychiatrist, had experience in developing or synthesizing candidate drug molecules. Dr. Tamminga admitted that she had no drug development experience at all, and Dr. Abraham's experience during this time period was extremely limited. *See DFF321.* In fact, it was Dr. Abraham's view that the replacement of any part of any molecule to form a new molecule would never be obvious. *DFF322.*

The foregoing supports the following additional findings of fact:

DFF321. None of Janssen's experts were qualified to contradict Dr. Wolff's testimony concerning drug development in the early 1980s. There is nothing in the record indicating that Dr. Meltzer, a psychiatrist, had experience in developing or synthesizing candidate drug molecules. Dr. Tamminga admitted that she had no drug development experience at all, and Dr. Abraham's experience during this time period was extremely limited. *See Tr. 224, l. 13 to 225, l. 15(M); Tr. 60, ll. 5-9 (T); Tr. 344, l. 3 to 346, l. 2 (A).*

DFF322. Dr. Abraham testified that the replacement of any part of any molecule to form a new molecule would never be obvious, because there would not be a reasonable expectation of success. *See Tr. 407, ll. 19-24.*

V. JANSSEN'S ATTEMPTED REBUTTAL

A. JANSSEN'S PRE-LITIGATION VIEW, INCLUDING THAT OF JANSSEN'S INVENTOR KENNIS AND HIS COLLEAGUE MEGENS, CONTRADICTS JANSSEN'S CURRENT POSITION THAT PIRENPERONE IS NOT AN ANTIPSYCHOTIC

Just in time for trial, Janssen trotted out a new theory as to why Pirenperone's antidopamine activity is not material——because Pirenperone allegedly was not an antipsychotic. Janssen bases its theory on the content of the Pirenperone patent (PX 80) and an argument that Pirenperone failed "multiple tests predictive of antipsychotic activity."

Janssen argues, *inter alia*, that Pirenperone was not an antipsychotic, because, if it were, Janssen would have identified it as such in the Pirenperone patent (PX 80). What Janssen disingenuously omits, however, is the fact that the Pirenperone patent was based upon patent applications filed in **1979** and **1980**, whereas the first data showing that Pirenperone had antipsychotic properties, *i.e.* strong dopamine antagonism, did not appear until **1981.** Dr. Dellenbaugh's testimony that, if Janssen viewed Pirenperone as an antipsychotic, the patent would have so stated, fails to admit that Pirenperone's potent antidopamine activity was recognized later.

Janssen attempts to support its position that Pirenperone is not an antipsychotic by referring to three abstracts relating to the testing of Setoperone, Pirenperone and other compounds. Janssen concludes that these abstracts teach

that Pirenperone is not an antipsychotic. Defendants dealt with this issue in DFF157-DFF173. To recap, there is no indication that Pirenperone was tested in any allegedly "predictive" tests in those articles, except (as argued by Janssen) the food reinforcement test. As Dr. McMillen testified, that test is "nonspecific" rather than predictive. *See DFF165*. Further, although the first such abstract (DTX-141) states "[u]nlike Pirenperone, …Setoperone also suppressed response by food reinforcement," that same language did not appear in the Janssen abstract from three months later (DTX-144). The later abstract simply stated that Setoperone "more so than Pirenperone . . . suppressed response control by the (food) reinforcer." As Dr. McMillen testified, this meant to one of ordinary skill in the art "that both drugs produced an effect, that Setoperone either produced a bigger effect or an effect at a lower dose." *See DDF167*.

Janssen quotes from Dr. Wolff's testimony at trial regarding the first abstract DTX-141, where he was asked if a person of ordinary skill in the art would go against Dr. Janssen's recommendation. Dr. Wolff replied, "perhaps not." What Janssen fails to tell the court is that its counsel specifically admonished Dr. Wolff *not* to read the later abstract (DTX-144) (Mr. Diskant: "In fact, Dr. Janssen repeated this essential [idea] in two other articles we won't review I have given to you. PX388 and 389." Dr. Wolff: "Okay. I won't review them."). It was the later abstract that indicated that Pirenperone in fact *had* activity in the food reinforcement test–the abstract that Dr. Wolff was told not to read. On redirect Dr.

Wolff was asked about that later abstract, and Dr. Wolff agreed with Dr. McMillen, that the later abstract did *not* teach that Pirenperone had no activity in that test. *See DFF167 and DFF168.*

A central problem with Janssen's new argument that Pirenperone is not an antipsychotic (and there are many) is that somebody forgot to tell the inventor, Mr. Kennis, and his colleague, Dr. Megens (who worked for Janssen in antipsychotic drug development in the early 1980s), about this theory. Neither agreed with Janssen's current contention that Pirenperone is not an antipsychotic. Indeed, their deposition testimony was exactly to the contrary.

Mr. Kennis characterized Pirenperone as a "neuroleptic," *i.e.*, an antipsychotic. *See DFF323.* Indeed, and according to the testimony of the '663 patent inventor Mr. Kennis, Pirenperone was tested by Janssen as an antipsychotic. Janssen did not further pursue Pirenperone as an antipsychotic only because of its "metabolic problem," described by Mr. Kennis as being due to the fact that the "keto group is reduced to hydroxy function." *See DFF125.*

REDACTED

Perhaps this is why Kennis and never appeared at trial.

Moreover, in 1996, prior to the filing of the present lawsuit, Mr. Kennis, along with his Janssen colleagues Mr. Vandenberk (his co-inventor of the '663 patent) and Drs. Megens and Awouters, authored a "retrospective" book chapter

relating to the development of antipsychotics that repeatedly identifies Pirenperone as a "neuroleptic" (*i.e.*, an "antipsychotic"). *See DFF153-DFF155; DTX-164; Parties' Stipulated Definition of "Neuroleptic;"* attached at *Janssen's Findings, App. A, p. ii.*

Even if one adopts Janssen's litigation-induced standard, the record establishes that Pirenperone was known by Janssen itself to possess properties that would have made it a candidate for development as an antipsychotic. *See, e.g., Section IV.A. of Defendants' FF/CL* (Janssen classifying Pirenperone as a neuroleptic, i.e., an antipsychotic; *DFF152-DFF156)*. Under either of Janssen's standards, its position cannot be sustained.

The foregoing supports the following additional findings of fact:

DFF323. Mr. Kennis characterized Pirenperone as a "neuroleptic," i.e., an antipsychotic. *See Kennis Dep., p. 217, l. 24 to 219, l. 16 (at p. 218, l. 23 to p. 219, l. 16 (DTX-94)*(identifying the structure designated in *PTX-94* (R47465) as Pirenperone, and confirming that the proposed pharmacology is "neuroleptic"); Parties Stipulated Definition of "Neuroleptic," attached to *(Janssen's Proposed Findings, App. A, p. ii.)*.

DFF324.

REDACTED

B. JANSSEN'S REQUIREMENT THAT A PRIOR ART COMPOUND MUST HAVE BEEN USED AS AN ANTIPSYCHOTIC IN THE CLINIC CONTRADICTS ITS POSITION BEFORE THE USPTO

Janssen asserted to the USPTO that a compound's dopamine antagonism, as determined by animal testing (the ATN (rat) test and the apomorphine (dog) test), was predictive of antipsychotic activity in humans, and that this was well-known to those skilled in the art. Indeed, Janssen obtained the '663 patent solely on the basis of these animal test data. *See, e.g., DFF69-DFF80.*

In this litigation, however, Janssen is telling a different, and inconsistent, story. Janssen maintains that obviousness cannot now be based on a showing that that the prior art compound Pirenperone possessed dopamine antagonism in these same animal models. Contrary to the arguments it made to obtain the patent, Janssen now argues that only those prior art compounds that were known to function as an antipsychotic in humans, and which possessed reduced EPS, are within the scope and content of the prior art. *See, e.g., JFF/CL ¶ 83.*

The only reason Janssen has selected as a standard the need for a prior art compound to have been used as an antipsychotic in the clinic is to argue that Pirenperone is not within the scope and content of the prior art. If one applies a standard consistent with the content of the '663 patent and Janssen's assertions during the prosecution of the '663 patent, however, animal testing is entirely sufficient to establish antipsychotic activity.

Defendants adduced an enormous amount of evidence and legal authority establishing that Pirenperone is within the scope and content of the prior art—prior art which is consistent with the prior art cited by the Patent Examiner, and which included art based solely on animal testing. *See, e.g., Section III.B.1. of Defendants' FF/CL.* While these proofs are sufficient, Defendants also established that the prior art recognized that Pirenperone possessed the critical property known to those skilled in the art (*via* Janssen's own admission to the USPTO) to be desired in an antipsychotic—dopamine antagonism *via* ATN testing. *See, e.g., DFF85-DFF91; DFF104.* Thus, using the same standard used by Janssen in obtaining the '663 patent, there is every reason to conclude that Pirenperone is within the scope and content of the prior art. Of course, Defendants further demonstrated that Pirenperone possessed other properties that would have been recognized by those skilled in the art to be desirable in an antipsychotic. *See, e.g., DFF92-DFF98; DFF105-DFF113.*

C. THE FACT THAT PIRENPERONE DID OR DID NOT HAVE ANTICHOLINERGIC ACTIVITY IS IRRELEVANT IN VIEW OF THE FACT THAT PIRENPERONE DID NOT CAUSE EPS IN HUMANS

1. The Goal of Those of Ordinary Skill Working to Develop Antipsychotics was Not to Develop an Anticholinergic Drug, but to Develop an Antipsychotic with Low EPS

In Paragraphs 111 through 153 of its *JFF/CL*, Janssen extensively argues that one of skill in the art in the early 1980s would have been looking for a drug with anticholinergic properties in order to develop an antipsychotic with low or no EPS, and that Pirenperone would not have been a logical starting point because it did not exhibit anticholinergic properties.

But one of ordinary skill in the art in the early 1980s had as an ultimate goal developing an antipsychotic with improved side effects, *i.e.* low EPS, and how one achieved that goal was irrelevant. *See, e.g., PX 276 (introduction).*

There really is no debate. A goal of antipsychotic drug development in the early 1980s was an antipsychotic that had no or reduced EPS. Such drugs were known as atypical antipsychotics. As Dr. Meltzer testified at trial, "the concept of an atypical, as I explained, was low EPS, and at least adequate antipsychotic [activity]." *See DFF325.* And, Dr. McMillen testified as follows:

> Q. And like the other people at the time who were trying to develop antipsychotic drugs you were trying to develop an antipsychotic drug with reduced--that would lead to reduced EPS. Correct?

A. Correct

See DFF326.

And Dr. Wolff testified:

Q. And it was an important goal in designing the new antipsychotic in the mid 1980s to try and reduce EPS, correct?

A. That's correct.

See DFF326.

Since Pirenperone was known not to induce EPS in humans, how and why Pirenperone achieved the goal of having low EPS would have been irrelevant to one of ordinary skill in the art. *DFF327*. The goal of low EPS had already been achieved by Pirenperone.

The foregoing supports the following additional findings of fact:

DFF325. Atypical antipsychotics have low EPS. As Dr. Meltzer testified at trial, "the concept of an atypical, as I explained, was low EPS, and at least adequate antipsychotic [activity]." *Tr. 255, ll. 12-13.*

DFF326. Drs. McMillen and Wolff testified that those of ordinary skill in the art in the early 1980's had reduced EPS as a goal in the development of new antipsychotics. *Tr. 504, ll. 21-25 (Mc)*; *Tr. 618, ll. 5-8 (W).*

DFF327. Since Pirenperone was known not to induce EPS in humans, how and why Pirenperone achieved the goal of having low EPS would have been irrelevant to one of ordinary skill in the art in the early 1980s.

2. It Was Undisputed by 1985 that Pirenperone was Known in the Prior Art to Have Very Low or No EPS in Humans

As Defendants have already discussed, Janssen safely tested Pirenperone in several hundred patients in need of psychotropic treatment. *See DFF106; PX 21.* There was no evidence that patients receiving oral doses of Pirenperone for use as a psychotropic ever experienced EPS. *See Section III.B.2.b.iv. of Defendants' FF/CL.*

One of the studies supporting this finding, by Monté *et al.*, specifically reported a very low incidence of tremors indicative of EPS in patients treated with Pirenperone. *See PX 21.* Moreover, even Janssen agreed that Pirenperone exhibited low or no EPS in humans. The 1983 paper by Ansseau *et al,* which included a Janssen scientist (Y. Gelders) as a co-author, explicitly stated that "[p]atients appear to tolerate Pirenperone well without sedative, extrapyramidal or anticholinergic side effects." *See DFF108.* Therefore, as Janssen itself acknowledged in 1983, Pirenperone would have been an answer to one of ordinary skill in the art in the early 1980s who sought a compound that had low EPS.

In its proposed findings (*JFF/CL ¶¶ 83 and 98),* and despite these studies, Janssen now attempts to paint the opposite picture for Pirenperone, *i.e.*, that patients treated with it experienced EPS. In support, Janssen points to an article about the intravenous use of serotonin antagonists (including Pirenperone and Ketanserin) in anesthesia. *See PX 384.* However, Janssen offered no evidence

other than this article, and when Dr. Wolff questioned the article's content during his cross-examination, Janssen's trial counsel immediately dropped that line of questioning. While it is correct that PX 384 reports that clinical investigation of the use of Pirenperone in anesthesia was abandoned because EPS had been observed, it is also correct, as Dr. Wolff pointed out at trial, that no dosage information is given for Pirenperone therein. *See DFF109-DFF110.*

Knowledge of the dosage at which a compound was given to a patient would be important in determining whether a compound causes EPS. *See DFF109 and DFF110.* This principle may be confirmed in connection with many compounds, including Ketanserin and Risperidone. For example, the article relied upon by Janssen gives a dosage range for Ketanserin, with the upper end of that dosage range (270 mg) being **27 times more** than the 10 mg of Ketanserin that Dr. Paul Janssen reported as being effective for the treatment of hypertension. *See DFF328; DTX-89.* In addition, according to the package insert for Janssen's Risperdal® drug product, Risperidone (the active ingredient in Risperdal®) causes EPS in a dose-dependent way, with EPS seen in up to one third of patients when the dose of Risperdal® is only slightly raised (by a factor of less than 2) from ≤10 mg/day to 16 mg/day. *See DFF328; PX 318.*

The foregoing supports the following additional finding of fact:

DFF328. Many compounds, including Ketanserin and Risperidone, can show EPS at high doses. For example, the article relied upon by Janssen gives a

dosage range for Ketanserin, with the upper end of that dosage range (270 mg) being 27 times more than the 10 mg of Ketanserin that Dr. Paul Janssen reported as being effective for the treatment of hypertension. *See DTX89*. In addition, according to the package insert for Janssen's Risperdal® drug product, Risperidone (the active ingredient in Risperdal®) causes EPS in a dose-dependent way, with EPS seen in up to one third of patients when the dose of Risperdal® is only slightly raised (by a factor of less than 2) from ≤10 mg/day to 16 mg/day. *See PX 318*.

3. The Anticholinergic Theory Was Not Alone

While Janssen argues that low EPS necessarily equates with anticholinergic activity *(See, e.g., 248, ll. 4-11 (M))*, the testimony of their own witness establishes that other viable theories existed in the early 1980s about how low EPS in antipsychotics could be achieved. *See Tr. 242, l. 14 to 243, l. 1 (M)*. Although Janssen cites work by other drug companies (including Eli Lilly) on clozapine derivatives as following the "anticholinergic model" (*See, e.g., JFF/CL ¶ 129, Tr. 249, l. 22 to 250, l. 15 (M)*), Lilly wrote an entire paper on the topic that does not once mention clozapine's anticholinergic activity. *See PX 749*.

Further, Janssen attempts to bolster its argument for the "dominance" of the anticholinergic theory and for the idea that "Janssen was virtually alone in …pursuing serotonin and dopamine antagonism" by stating that only a "few" papers contained "cryptic" suggestions that serotonin was involved in reducing

EPS in antipsychotics. *See JFF/CL ¶¶ 131 & 134.* Janssen's assertion is simply not correct. For example, the introduction to the 1978 paper by Lai *et al.* (*PX 37*), relied upon extensively by Janssen's witness Dr. Meltzer, states at page 347 that "[a] **body of literature** suggests that **DA-serotonin** interactions may be involved in various brain functions." (emphasis added). ***Nine* papers** from ***eight* different research groups** comprise the "body of literature" referred to in the Lai *et al.* paper. *See PX 37.* Clearly, Janssen was not "virtually alone." Moreover, Lai *et al.* concluded that "our studies have shown that three neuroleptic agents which are regarded to possess low EPS potential in man were highly effective in inhibiting ^{3}H-serotonin binding to its receptors." *See PX 37, p. 352.*

Another way in which Janssen attempts to bolster its argument that anticholinergic was the dominant theory, and downplay the prominence of the combination dopamine and serotonin theory, is by using improperly truncated sentences which have been completely removed from their context. A particularly egregious example of this occurs in *JFF/CL ¶ 135*, where Janssen improperly quotes a mutilated version of the first half of a sentence in the 1978 paper by Sulpizio *et al.*: "**. . .**[I]nvestigations into the anti-dopamine and anticholinergic activity of clozapine are obviously important in elucidating its overall pharmacological profile…." *See PX 38, p. 1445.* The full sentence in the Sulpizio *et al.* paper conveys quite a different meaning: "While investigations into the anti-dopamine and anticholinergic activity of clozapine are obviously important in

elucidating its overall pharmacological profile, our data suggest that the study of clozapine's **anti-serotonin activity** is of ***equal importance***." (emphasis added).

Additionally, Sulpizio *et al.* further state that:

> The existence of a relationship or balance between dopamine and serotonin in the mediation of tremor has been postulated by several investigators.

See PX 38, p. 1445.

Thus, the work of Sulpizio *et al.* and the results of *four other* research groups discussed in Sulpizio *et al.* entirely undercuts Dr. Meltzer's testimony that in 1985 there were no theories associating serotonin with low EPS in antipsychotics. *See Tr. 246, l. 24 to 247, l. 19 (M); JFF/CL ¶ 138.* Moreover, the 1978 Sulpizio *et al.* paper provides a more accurate view of the early 1980s than Dr. Meltzer's own non-prior art hindsight retrospective paper (1989), which was used extensively by Janssen at trial for its purported teachings about "the state of the art" of atypical antipsychotic theory in 1985. *See Tr. 256, l. 10 to 262, l. 18 (M).*

The fact remains unrebutted that Janssen did not ascribe to the anticholinergic theory and told the world that fact. *See DFF182.* And, Setoperone, which is Janssen's next choice as a "lead compound" after Clozapine, was reported by Janssen to be completely devoid of anticholinergic activity. *See DFF183.*

The foregoing supports the following revised finding of fact.